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A REVIEW OF CENTRAL NERVOUS SYSTEM (CNS)/COGNITIVE EFFECTS DUE TO BLAST

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14. ABSTRACT

An extensive literature review of central nervous system (CNS)/cognitive effects due to blast overpressure has been performed to support the assessment of human effects due to flashbang devices. Epidemiology and laboratory data have shown evidence that correlates CNS injuries to blast, but the primary mechanism of injury on the gross and molecular level is not understood. Laboratory data have suggested blast induced brain injuries have similarities to traumatic brain injuries (TBI). Full body blast test animals have shown an increase in certain molecules linked with nerve cell apoptosis and cognition dysfunction. Data also suggest blast overpressure can cause adverse cognitive effects resulting in executive deficit similar to that produced in other TBI models. Long term cognitive effects of blast include disturbances in attention and memory, and a delayed reaction time in problem solving. Veterans returning with blast injury also exhibit post concussion symptoms similar to those seen in other forms of TBI. Since the mechanism relating blast and cognitive deficit is not known, the authors recommend that an effort should characterize of CNS/cognitive effects due to blast since potential CNS injuries must be taken seriously, and data suggest a correlation between blast and cognitive effects.

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Central Nervous System, cognitive effects, blast, traumatic brain injury, blast overpressure, blast injury, blast injury mechanisms, cognitive recovery, head injury, intracranial pressure, CNS

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Executive Summary

An extensive literature review of central nervous system (CNS)/cognitive effects due to blast overpressure has been performed in support of the assessment of human effects due to flashbang devices. Epidemiology and laboratory data have shown evidence that correlates CNS injuries to blast, but the primary mechanism of injury on the gross and molecular level is not understood. Laboratory data have suggested blast-induced brain injuries have similarities to traumatic brain injuries and mild traumatic brain injuries (TBI and mTBI). Blasts have been shown to start cell signaling cascades which end with nerve death in the brain. Full body blast test animals have shown an increase in certain molecules linked with nerve cell apoptosis and cognition dysfunction. It is not fully understood if the activation of these cell signal cascades is a result of direct blast damage to the brain or a result of tissue injury in other parts of the body traveling to the brain. Data also suggest blast overpressure can cause adverse cognitive effects resulting in executive deficit. Laboratory data have shown blast overpressure causes significant cognition dysfunction in test animals. Researchers observed a memory deficit which was linked to hippocampus damage in the brain. The memory dysfunction was also observed to be similar to that produced in other TBI models. Long term cognitive effects of blast include disturbances in attention and memory, and a delayed reaction time in problem solving. Veterans returning with blast injury also exhibit post concussion symptoms similar to those seen in other forms of TBI. Little is known in the mechanism relating blast overpressure and cognitive deficit.

It is recommended that an effort should be continued for the multisensory stimuli program to pursue definitive characterization of CNS/cognitive effects due to blast for the very reason that any potential CNS injuries must be taken very seriously, and data have suggested a correlation between blast and cognitive effects. The threshold for permanent injury is still not known. It is likely that the mechanism for cognitive effects due to flashbang may be at the neuronal, molecular, cellular or biochemical level as opposed to the traumatic outcomes. Field data have corroborated long-term cognitive deficit effects due to blast. For non-lethal weapons, it is the immediate reversible effect that is of high interest, but any long-term effect must be avoided. At present, it is recommended the use of small animals is the appropriate path for studying mechanisms of immediate and midterm executive deficit effects due to blast at the levels produced by current and evolving flashbang devices. Tests involving human volunteers must be considered very carefully in light of the small animal results.

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1.0 Introduction

Non-lethal technologies are having an increasing impact on war fighting, peace support operations, and civil policing. The purpose of these technologies is to incapacitate targets with temporary and reversible effects. When designing these weapons and developing protocols for usage, it is therefore necessary to know which thresholds must be reached to achieve the desired effect and which must not be crossed to avoid permanent damage. This report is an extensive literature review conducted to determine the effect exposure to blast overpressure has on brain injury and any resulting cognitive dysfunction.

Beginning in 2004, L3-Titan (formerly Titan) has been supporting the Joint Non-Lethal Weapons Directorate Human Effects Center of Excellence (JNLWD/HECOE) effort in developing methodologies in assessing the effects from non-lethal multisensory stimuli (MSS) flashbang devices. Field tests and modeling studies have been performed in 2004 and 2005 for the prediction of the four tangible effects, namely, blast, noise, burn and optical effects due to flashbang, with criteria and models assembled and evaluated.

For blast injury assessment, the lung has been traditionally selected as the target organ for human effect assessment for occupational protection where extensive research has been undertaken by the US Army Medical Research and Materiel Command (MRMC) for over 50 years. Validated by large animal data, the INJURY model developed by Jaycor (now L3-Titan) under MRMC sponsorship has become the standard method for assessment of primary blast injury (PBI). Based on INJURY predictions using the HECOE field data collected from 2004-2005 as inputs, the probability of blast lung injury due to flashbang devices is extremely low, especially when thermobaric formulations are used.

Blast carries an intangible “shock and awe” component that is very difficult to quantify. Executive deficit has been observed from veterans exposed to blast. For non-lethal weapon development, blast is acceptable only if usable and reversible cognitive effects due to blast can be generated with quantifiable criteria while ensuring that any permanent damage thresholds are not exceeded. The conflicts in Afghanistan and Iraq have caused soldiers to suffer “blast and related” injuries that have not been seen in large numbers in recent times. A combination of better body armor and an enemy that is employing crude, but massive explosive devices has caused soldiers to survive exposure to extreme blasts. As a result, there is observed a higher incidence of blast injuries, including head/brain injuries.

In a recent study of traumatic brain injury patients at Walter Reed Army Medical Center and National Naval Medical Center, blast was responsible for 66% of the TBI which required neurosurgical care (Neal et al., 2005). The Joint Theater Trauma Registry, compiled by the U.S. Army Institute of Surgical Research, reports that 22% of all wounded soldiers, which have passed through Landstuhl Regional Medical Center in Germany, had injury to the head, face, or neck. This is in contrast to Vietnam, where 12 to 14% of all combat casualties had brain injury (Okie, 2005).

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A blast is characterized by a sudden increase of air pressure (overpressure) followed by a decrease in pressure and blast wind. In an open field, the energy of the blast waves decrease exponentially from the origin of the blast. However, indoors, blast waves rebounding off walls and rigid objects result in complex pressure waves which may enhance the original blast wave (DePalma et al., 2005).

Injury due to blast is usually categorized in four modes, primary (direct effects of pressure), secondary (effects of projectiles), tertiary (effects of wind), and quaternary (burns, asphyxia, and toxic inhalants). Primary blast injury (PBI) is most often seen in organs which are vulnerable to changes in pressure, namely the rupture of the tympanic membrane in the ear, pulmonary damage, and rupture of hollow viscera. The eardrum can rupture at pressures 5 psi above normal atmospheric pressure, which is much lower than the thresholds for blast lung injuries. Research on blast injuries to the head and CNS has been very much limited.

Gas filled organs are more susceptible to blast pressure than solid organs. The rapid compression from the blast causes the gas and blood contained in these organs to be forced against the various compartments and cell walls, causing them to rupture (Rossle, 1950; Clifford et al., 1984; Phillips III and Richmond, 1991; Sharpnack et al., 1991; Brown et al., 1993; Elsayed, 1997). Particularly for the thorax, the traumatic loading of the chest wall by the blast causes a shock wave that propagates into the lung at a very low speed, and the pressure difference across the alveolar-capillary interface causes disruption, hemorrhage, pulmonary contusion, and subcutaneous emphysema. Pulmonary injuries can be life-threatening if extensive (Mayorga 1997; Stuhmiller 1997). Over the last two decades, a large part of the research in primary blast injury has been conducted on the more susceptible organs (ears and lung).

To support the JNLWD/HECOE effort in exploring the potential cognitive effects due to blast, an extensive literature review effort has been carried out. The findings are summarized in this report. This will include both the observed injury from blast and cognitive dysfunction due to brain injury. Recommendations for future effort are given.

2.0 Definitions

Research on blast trauma to the brain has borrowed many of the concepts and hence terminologies from the traditional TBI studies mostly conducted by the automotive researchers that have also extended into impact sports injuries. It should be noted that blast is a shock wave type insult with high rise rate and short duration, usually less than a few ms. In contrast, the insults from car crash or impact type loadings have much slower rise rate with longer durations, like 10-40 ms. Nevertheless, it has been claimed that observed outcomes and symptoms due to blast injuries to the head share many similarities to those of closed head TBI. Depending on the magnitude of the insult, different levels of traumatic brain injury can occur. Mild TBI (mTBI) is not usually associated with visible abnormalities on brain images. Mild TBI occurs in a brain injury which

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causes a loss of consciousness lasting less than 1 h or amnesia lasting less than 24 h. Concussion is usually associated with mTBI. Moderate TBI produces a loss of consciousness of 1 to 24 h or amnesia lasting between one and seven days. Severe TBI is defined as a loss of consciousness of more than 24 h or amnesia lasting more than one week. Moderate and severe TBI can also be recognized in magnetic resonance images by hemorrhages and swelling of the brain (Okie, 2005).

3.0 Evidence of Brain Injury due to Blast Overpressure

3.1 Observable Brain Injury due to Blast

Very few experiments have been conducted where the brain of the test subjects was investigated after sustaining brain injury due to blast. In a study conducted by Bauman et al. (2005), *Sus scrofa* (swine) and *Ovis aries* (sheep) were exposed to explosive charges in a confined space. After exposure, the animal brains were removed and prepared for histology. Fiber degeneration in the white matter of the forebrain and cerebellum was seen in both pigs that died immediately after exposure and pigs that survived 2 weeks. Fiber degeneration was also seen in the forebrain, olfactory and optic tracks, and superior colliculus in the sheep. Bauman et al. reported that this is the first report of blast directly linked to brain injury.

Knudsen and Oen (2003) investigated brain trauma in whales killed by neurotrauma through an intrabody detonation of 30 g penthrite mounted on harpoons. Depending on the proximity of the detonation to the brain, the extent of brain damage differed. Detonations occurring less than 1 m from the brain resulted in skull fractures and either total disintegration of the brain architecture or massive intracerebral hemorrhages. Detonations occurring farther away produced hemorrhaging mainly under the brainstem and cervical spinal cord and some small localized meningeal hemorrhages on the top of the cerebrum. Microscopic analysis reported deep white matter injuries.

Cernak et al. (2001a) also reported white matter injury in rats exposed to blast overpressure. Rats were exposed to a blast wave with a mean peak overpressure of 338.9 ± 9.1 kPa for a duration of 52 ms to the whole body of the rat or an overpressure of 440 kPa with a duration of 50 ms to the right middle thoracic region. These blast levels produced PBI on the rats. In both cases, evidence of neuronal injury was seen in the hippocampus (i.e., area of brain thought to transition short-term memory to long-term memory). These injuries consisted of vacuolated cytoplasm and lamination of myelin in the severely affected cells (Cernak et al., 2001a).

The damage seen from blast-induced TBI share many similarities with acceleration/ deceleration induced TBI (dTBI) which occur from shearing or impulsive forces (De Girolani et al., 1994). dTBI is characterized by few findings at gross examination except for hemorrhages in various regions of the brain, namely the white matter of the cerebrum, basal ganglia, and pontine region.

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Another significant feature of dTBI is diffuse axonal injury (DAI) which is characterized by the rupture of axons in the cerebral white matter, the brainstem, and in the cerebellum (McIntosh et al., 1996).

3.2 Primary Mechanisms of Brain Injury

The mechanism of blast energy transfer to the brain is still not well understood. It is possible that the energy is transmitted to the brain through (1) direct energy transfer through the skin and skull from the blast, (2) the rapid acceleration of the head from the blast, or (3) wave propagation through the muscle and body structure, such as the cardiovascular system or the spinal cord, as a result of sudden impulsive overload.

3.2.1 Direct Energy Transfer

Under separate research sponsored by MRMC to explore blast effects on the head and brain, we have performed simulations using an anthropomorphic finite element model of an average head subjected to a strong freefield blast overpressure loading. This model was constructed using CT scans of a human head and was validated in skull fracture studies (Bandak et al., 1995). It was found that even when exposed to a strong blast overpressure that would cause blast lung injury (700 kPa peak), there was very little deformation to the skull. The rigidity of the skull provides a barrier between the brain and the blast wave, allowing very little direct energy transfer. Blast overpressure applied to the scalp/eyes directly over openings in the skull, such as the superior orbital fissure, also resulted insignificant amounts of energy transfer.

3.2.2 Acceleration Effect

An acceleration of the head, however, will create a coup/contrecoup pressure gradient inside the head and brain. This is primarily due to the total body acceleration effect on the brain, which essentially behaves like a fluid medium inside the skull. Most studies on acceleration effects on TBI are carried out for car crash or impact conditions where the acceleration duration is much longer than that for blast. Zhang et al. (2001) reported that the intracranial pressure magnitude is largely a function of the translational acceleration of the head while the maximum shear stress is more sensitive to rotational acceleration. Zhang et al. also predicted intracranial pressures which resulted in injury (mTBI or concussion); 90 ± 24 kPa for coup pressure, 76 ± 25 kPa for contrecoup pressure (Zhang et al., 2004). Ward et al. reported a coup pressure of 235 kPa for serious brain injury (Ward et al., 1980).

Usually, when considering threshold injury values, the peak pressure and duration have to be considered within the valid range. The threshold estimates reported above were calculated from longer duration events (20-30 ms) when compared to a blast wave (1-2 ms). The longer the duration the lower the injury

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threshold usually becomes. An overpressure of 770-1100 kPa is expected to be lethal with a duration of 3 ms, but a lower pressure of 260-360 kPa is lethal with a duration of 400 ms (Altmann, 2001). Therefore, the reported pressure injury thresholds for head injuries observed from long duration studies may not be valid for blast-type conditions. There has yet to be any study, to our knowledge, in determining the pressure thresholds for closed head injury for a blast case. It should also be noted that tissues fail mechanically by shearing, which is a condition that a long-duration insult would likely produce. It is still unclear how a high peak pressure with minimal strain would injure the brain material mechanically.

Using our closed head finite element model, coup/contrecoup pressures in the head were calculated using strong and weak blast overpressure conditions. The strong blast condition would produce lung injury while the weak blast case represents pressures encountered a few feet from a flashbang device that would not cause lung injury. All blast durations were 1 ms. The peak brain pressures calculated are shown in Table 1. Incidentally, the peak coup/contrecoup pressure values calculated for the weak blast case are in the range of thresholds for concussions based on field data reconstruction studies for football helmet impact injuries (Zhang et al., 2004). Nevertheless, it is cautioned that no criteria for head injury due to blast have been established.

Table 1. Calculated Intracranial Pressures from Blast Overpressure

	Peak Coup Pressure	Peak Contrecoup Pressure
Strong blast (800 kPa)	900 kPa	-300 kPa
Weak blast (60 kPa)	120 kPa	-55 kPa

3.2.3 Wave Transfer Through Blood Vessels

A number of hypothesis have been put forth to explain direct brain damage following blast pressure exposure of the body. One theory is that blast waves are transmitted to the brain via blood vessels and cerebrospinal fluid resulting in increased pressure on the brain cells and capillaries, especially the brainstem (Mott, 1916; Stewart et al., 1941; Cramer et al., 1949; Cernak et al., 2001a). It has also been proposed that the blast-induced compression of the thorax and abdomen creates an intense venous backpressure, which leads to intracerebral hemorrhages (Rogers, 1945; Wood & Sweetzer, 1946).

Knudsen and Oen (2003) state that after detonation, an oscillating pressure wave propagates through the whale body and when it reaches the CNS it likely generates a high-pressure differential within the blood vessel. This would rapidly change the intracranial pressure and cause rupture of blood vessels in the meninges and brain tissue. This is supported by the presence of hemorrhages subependymal. They also reported many more microscopic

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hemorrhages than seen grossly, due to the large number of capillary and postcapillary venules which were damaged.

3.2.4 Air Emboli

Air emboli have been seen in the Circle of Willis after some animals are exposed to blast overpressure. It is unclear if the air pocket seen is an artifact of postmortem brain preparation or due to lung damage. A study by Dodd et al. (1997) reported 29% incidence of air emboli. An unpublished test by Johnson, at Walter Reed, exposed pigs to blast pressure via a shock tube and no animal had evidence of air emboli (Mayorga, 2002).

3.3 Secondary Mechanisms – Molecular Effects

Along with physical changes to the brain tissue (hemorrhages, contusions, etc.), research has shown that changes on the molecular level also affect TBI. Studies at Walter Reed Army Institute of Research observed that animals that survived blast exposure would expire after a period of time. This was thought to be due to oxidative stress occurring as a result of the blast. Oxidative stress is the state where there is an imbalance in the oxidants and antioxidants. This leads to cell damage, dysfunction or death (Elsayed & Gorbunov, 2003). As described by Elsayed and Gorbunov, blast exposure causes lung damage which interferes with the blood's oxygen carrying capacity. This leads to hypoxia, antioxidant depletion, and then oxidative stress.

Particular to the brain, evidence suggests that radial oxygen species (ROS) are involved in the pathogenesis of neuronal death. After cerebral ischemia, ROS are generated inside mitochondria. ROS then start a signal cascade resulting in DNA damage, apoptosis and cell death. Within this signal cascade, a receptor (N-methyl-D aspartate receptor) is also activated which, together with nitric oxide (NO) and oxygen radicals, produces OH^{-}. This subsequent OH^{-} production directly damages lipids, proteins, DNA, and leads to cell death (Hall, 1993; Hall & Braughler, 1993; Awasthi et al., 1997; Cernak et al. 2000; Sugawara et al., 2004). The degree of oxidative stress has been closely related to the severity of brain injury and has been suggested as a marker for degree of TBI (Tavazzi et al., 2005). There are numerous studies showing the beneficial role of antioxidants and free radical scavengers in the treatment of TBI (Braughler & Hall, 1992; Inci et al., 1998; Cernak et al., 2000; Moochhala et al., 2004).

A study of indirect neurotrauma patients diagnosed with primary blast injury showed a significant decrease in plasma total magnesium values for two days post trauma and a significant increase of superoxide anion generation for seven days post trauma. Experimental data have shown that magnesium depletion is closely linked with neurological deficit and cell death (Vink et al., 1996). Magnesium is essential for the stability and normal function of cell membranes (Birch, 1993). Cernak et al. (2000) concluded that there is a significant correlation between the reduction of ionized magnesium and the

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increase of oxidative stress. This suggests that insufficient magnesium balance provides the formation of ROS and modifies antioxidant defense following TBI.

Another study by Cernak et al. analyzed the central nervous system response to pulmonary blast injury. A 304 kPa blast to the middle thoracic region of rabbits resulted in an increase in the levels of lipid peroxidation products and water content in the medulla oblongata. Glucose and lactate concentrations were elevated in the brain structure, and an increased PCr/ATP ratio suggested intensive energy consumption. The magnesium concentration decreased significantly; however, calcium and zinc concentrations remained normal. A blast wave focused to the lungs resulted in significant impairment of energy metabolism in the brain. Cerebral edema, electrolyte and mineral imbalance, and increased lipid peroxidation product levels demonstrate the disruption of cellular functions in the brain (Cernak et al., 1996).

Animal tests on rats exposed to blast overpressure have shown a significant increase in NO concentration for 24 h after injury (Cernak et al., 2001b). Along with playing a role in the pathological process of cerebral ischemia and TBI, NO has been identified as a neuronal messenger. It has roles in blood pressure regulation, neuronal signaling, and immunological functions. A number of studies have also indicated that NO is involved in avoidance (Baratti & Kopf, 1996; Telegdy & Kokavszky, 1997), spatial and motor learning (Qiang et al., 1997; Hawkins et al., 1998). Following the blast injury, the rats had cognitive impairment along with an increase of NO production in the brain. This supports data from Wada et al. (1999) in which inhibiting NO production has a beneficial effect on sensorimotor outcome after TBI.

Changes in the nerve cytoskeletons are often seen in diffuse axonal injury (DAI) from rotational acceleration. One of the main components for maintenance, support, and transport along nerve axons are neurofilament proteins (NFH). In neurodegenerative diseases, phosphorylated NFH which usually travel down the axon, accumulate in tangles. To investigate the effect of blast on NFH, rats were exposed to blast pressure waves. Dissected brains showed no hemorrhages or tissue lesions. Abnormal distributions of neurofilaments were seen one week following exposure. The distributions were similar to those observed in the nervous system of patients with neurodegenerative disorders, including Parkinson's and Alzheimer's diseases. Blast exposure induced a redistribution of p-NFH, which is linked to a high risk for delayed nerve cell loss (Saljo et al., 2000).

Blast exposure was also found to activate both microglia and astrocytes. These cells were found in the regions of the brain which contained altered neurofilament patterns. Activated microglia and activated astrocytes are implicated in the formation of tau2-immunoreative neurotic plaques in Alzheimer's disease (Saljo et al., 2001). A follow up study reported that a single intense noise impulse causes diffuse brain injury and both nerve and glial cells were damaged. Pre-existing damage of nonhealed nervous tissue was also found to reduce the threshold of injury from future blasts (Saljo et al., 2003).

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4.0 Cognitive Effects Of Brain Injury/Concussion

4.1 Cognitive Effects from Blast Injury

Cernak et al. (2001b) conducted studies on the direct correlation between blast damage and cognitive impairment. However, as demonstrated by numerous studies, brain injury from blast overpressure resembles diffuse axonal injury. There has been a large amount of research performed quantifying the cognitive effects of DAI. Using methods such as fluid percussion injury models, controlled cortical impact models, controlled concussion models, and impact acceleration models, repeatable brain injuries can be replicated (Cernak, 2005). There is some implicit assumption that the outcomes observed from percussion-induced DAI would also occur in blast-induced DAI.

In the first study conducted by Cernak et al. (2001b) to determine the cognitive deficits due to blast injury, rats were trained to achieve active-avoidance response (AAR) in a maze. After the rats were well trained, the blast group of rats was subjected to a 338.9 kPa whole-body blast that would produce pulmonary injury. There was a highly significant and sustained decline in rat postinjury AAR performance. The performance decline was seen 3 hours post-trauma to 5 days post-trauma when the rats were sacrificed. There was a significant linear relationship between the blast injury severity and AAR performance. The active avoidance latency and the escape response latency were also significantly increased. These results suggest that the rats developed a significant memory deficit following exposure to the blast.

Cernak et al. (2001b) performed a follow-up study in which rats were either exposed to whole-body blast or local (chest only) blast. The whole-body blast overpressure was 338 kPa and sustained for 52 ms, while the local blast overpressure was 440 kPa sustained for 50 ms. As in the previous study, the whole-body blast rats' performance of AAR was significantly reduced through the 5-day study period. The local exposure rats' performance was reduced during the first 3 hour period post-trauma, however, it returned to normal levels after 24 hours. Examinations of the hippocampus of both groups of rats suggest that ultrastructural and biochemical changes there caused cognitive deficit. The changes in this study were comparable to the findings of other studies using various traumatic injury models to test memory deficits, such as fluid-percussion injury, controlled cortical impact in mice, and diffuse axonal injury in rats. The majority of these studies emphasize a close relationship between memory dysfunction and hippocampal neuropathology after TBI (Cernak et al., 2001a).

Change in cognition and behavior has also been seen in combat veterans returning with a history of blast concussion. These soldiers often have symptoms affecting several areas of brain function. Common symptoms are headaches, sleep disturbances, and sensitivity to light. Cognitive changes included disturbances in attention, memory, or language, as well as delayed reaction time during problem solving. Behavioral changes often expressed are mood changes, depression, anxiety, impulsiveness, emotional outburst, or inappropriate laughter (Okie, 2005).

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In a study of combat veterans returning from Iraq injured by blast, a number of patient cases were reported. In one case, a patient reported a lapse of memory of the blast and immediately after, followed by an extended period of postinjury confusion. While the cognitive function of the patient was intact, testing revealed mild processing speed deficits. In a second case, a veteran receiving a mortar wound reported cognitive difficulties as well as mood disturbance. Neuropsychological evaluation revealed mild impairments in processing speed, attention, and executive abilities (inhibition and cognitive flexibility). Another veteran wounded by a mortar round was tested to find impairments in attention, executive functions, and processing speed (Belanger et al., 2005).

A study by Trudeau et al. (1998) analyzed the electroencephalograms of veterans with and without a history of blast concussion. A difference in the discriminate score between veterans with and without blast concussion was reported. In the group with a history of blast, in each case, the blast concussion was relatively mild and medical evaluation and attention was not sought for. A significant number of the blast group had attentional symptoms and attentional dysfunction also. The authors concluded that mild concussion due to blast could produce mTBI as well as a prolonged postconcussive syndrome that in turn could influence the clinical course of post combat posttraumatic stress disorder (PTSD). Postconcussive syndrome and combat PTSD both have cognitive and behavioral symptoms in common. These include hyperactivity, memory deficits, fatigue, increased sensitivity to noise and light, insomnia, irritability, decreased concentration, and anxiety (Trudeau et al., 1998).

4.2 Short Term Cognitive Effects of mTBI/Concussion

A study was conducted to measure the immediate neurocognitive effects of mild TBI and then track the immediate and prolonged course of recovery after injury. The Standardized Assessment of Concussion (SAC) was used to immediately assess athletes who sustained mTBIs during competition or practice. The SAC is a brief screening test designed for the neurocognitive assessment of concussion by a non-neuropsychologist. It requires approximately 5 min for assessment of cognition, orientation, immediate memory, concentration, and delayed recall summing to a total composite score of 30 points. Immediately after injury, the mean SAC score for all injured subjects was significantly less than the baseline score. Subjects that suffered loss of consciousness (LOC) were the most severely impaired while subjects who suffered no LOC or posttraumatic amnesia (PTA) suffered the least. The mean SAC score for injured subjects 15 min after injury remained significantly below baseline value. The results from the immediate memory and delayed recall subtests of the SAC were significantly below baseline while no significant deficits were detected in the orientation and concentration subtests. There was no significant impairment detected 48 hours or 90 days after injury. It was concluded that subjects who experienced “ding” injuries (concussion without LOC

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or PTA) exhibited significant deterioration from preinjury baselines levels of cognitive function. Subjects who experienced a brief period of PTA after injury were more immediately impaired than those who did not experience PTA, and subjects who experienced LOC displayed the most severe neurocognitive impairment immediately after concussion. Injured subjects without PTA or LOC displayed the fastest recovery, while subjects with LOC remained more impaired (McCrea et al., 2002).

The immediate effect of concussion on reaction time was investigated using the Automated Neuropsychological Assessment Metrics test (ANAM) (Warden et al., 2001). The ANAM tests simple reaction time, continuous performance, mathematical processing, memorization, matching, and delayed memory. Subjects were military cadets at the United States Military Academy at West Point. They were tested before injury, 1 hour within injury and 4 days postinjury. The mean simple reaction time both 1 hour (315 ms) and 4 days (342 ms) postinjury were significantly higher than the baseline (254 ms). All other subtests of the ANAM showed no significant difference compared to baseline after 4 days. No cadet returned to baseline reaction time values by the time he returned to contact sports. The data does not indicate how long the recovery time would be. A study of high school football players reported no significant change in reaction time 4 months post injury (Daniel et al., 1999).

4.3 Long Term Cognitive Effect on mTBI/Concussion

Research has shown that mTBI is commonly presented as a number of imprecise perceptual symptoms without any diagnosable structural change in the brain (Kibby & Long 1996; Margulies, 2000; Milman et al., 2005). Injured patients report a number of signs such as headaches, dizziness, fatigue, irritability, memory problems, and emotional liability which are categorized under the term post concussion syndrome (PCS) (Levin et al., 1987; Kibby & Long, 1996). Most of the signs are called “late symptoms” because they are expressed days and weeks following injury. However, two of the symptoms, headache and dizziness, occur immediately as well as during recovery (Ryan & Warden, 2003). Patients with mTBI and persistent PCS have a high incidence of temporal lobe function deficits, which involves the hippocampus and related structures. Although the existence of PCS is well accepted, a definite biological marker for cognitive impairments that occur after mTBI is still missing. A number of mechanisms for the development of PCS have been proposed (Arciniegas et al., 1999; Albensi, 2001; Henninger et al., 2005)

It has been recognized through many studies that TBI is associated with significant and enduring cognitive deficits (Hamm et al., 1993). The relationship between the degree of injury and the extent of cognitive impairment is often evaluated using animal testing (Milman et al., 2005). Hamm et al. (1993) conducted a study to determine the effects diffuse axonal injury has on cognitive dysfunction. Rats were injured using fluid percussion then tested 11-15 days following injury. Results showed that injured rats did not have a deficit in learning

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or memory following a moderate level DAI. Injured rats showed a significant deficit in performance tasks (Morris water maze) which is known to be sensitive to hippocampal damage. It was concluded that injured animals are not impaired in their ability to learn a fixed association between the environment and a response. However, injured animals are significantly impaired on tasks that require a flexible response, which is most likely due to hippocampal dysfunction.

Milman et al. (2005) attempted to model human mTBI (as opposed to previous studies of severe TBI) by injuring mice with a weight-drop model. It was found that this model of mTBI induces a specific, significant, and long-term learning and memory impairment as well as depressive-like behavior in mice. The mice showed no dysfunction in reflex, balance, exploration, strength, locomotor activity, and swim speed. This supports previous research suggesting deficits in learning and memory common to humans with mild and moderate brain injury (Rimel et al., 1982; Strugar et al., 1993). The injury to the mice resulted in a persistent cognitive impairment starting a month after injury, along with a depressive state starting within the first week postinjury. Significant differences in performance were observed between injured and control mice in the swim T-maze and the passive avoidance test starting at day 30.

In a similar study, Henninger et al. (2005) developed a rat model for closed head human concussion injury using a weight drop device. The key features of human mTBI that were developed in this rat model were loss of consciousness, cognitive impairment, and minor brain damage. Immediately after impact, the test animals lost their muscle tone and righting reflex response. Corneal reflexes returned after 4.5 ± 3.0 min, whisker response returned after 6.1 ± 2.9 min, and righting reflex returned after 11.4 ± 8.2 min. These times were significantly longer then the times of control animals. Each animal then swam without difficulty. Injured animals spent significantly longer times finishing a Morris water maze then controls which suggests an impairment of spatial learning. After 9 days, there were no apparent DAI in the brain. There was a significant loss of hippocampal and cerebrocortical neuronal cells which may explain the impaired spatial learning.

4.4 Risk of Repeated mTBI

An emerging hypothesis is that repeating mTBI (rmTBI) may cause cumulative damage to the brain, which could ultimately result in memory and learning dysfunction. *In vitro* studies of hippocampal cells were studied to determine their response to cumulative damage. It was reported that repeated mild injury causes increased the amounts of cellular damage when compared to single insults of the same magnitude. While no evidence is available yet, one hypothesis is the pathways of cellular degradation differ between single and multiple TBI (Slemmer et al., 2002).

There have been widely divergent results associated with rmTBI on mice cognition studies. DeFord et al. (2002) reported that multiple mild impacts produced learning/memory impairments in wild-type mice. Uryu et al. (2002) found wild-type mice resistant to learning/memory deficits. In a third study by

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Laurer et al. (2001), multiple impacts on mice induced a stronger effect on motor function than cognitive functions. Creeley et al. (2004) reported a reversible loss of consciousness, a contracoup brain injury, and cognitive impairment in their series of tests. Parts of the divergent results have been attributed to a lack of standardization of testing.

In a recent study by Longhi et al. (2005), there were no reported cognitive deficits in sham-injured or mice that were concussed only once. Mice subjected to a second concussion within 3 to 5 days exhibited significantly impaired cognitive function. However, when the interconcussion interval was extended to 7 days, there were no cognitive deficits observed. All concussed mice showed transient motor deficits. Mice subjected to a second concussion within 5 days demonstrated a more pronounced vestibulomotor dysfunction. Greater axonal injury in subcortical white matter, fimbria, hippocampus, and hypothalamus were also seen in mrTBI mice.

4.5 Models of Cognitive Recovery

The majority of research predicting the recovery of cognitive dysfunction due to mTBI are long term studies (over 6 months). Many patients have spontaneous improvement within 3 months of injury. However, a subgroup of patients, estimated at 20%, continues with symptoms for 6 months or longer. There is little experience to predict who will experience persistent symptoms. An analysis of patients with mTBI concluded that there is no correlation between prediction of functional outcome and various indices (demographic and heath data, neuropsychiatric outcome measures, frequency of somatic complaints, and rate of return to work) (McCullagh et al., 2001).

5.0 Discussion

Epidemiology and laboratory data have shown evidence that correlates CNS injuries to blast, but the primary mechanism of injury on the gross and molecular level is far from being understood. Laboratory data have suggested blast-induced brain injuries have similarities to TBI and mTBI. Strong evidence was found supporting that blast can cause brain injury ranging from lesions and hemorrhaging to nerve degeneration. Blasts have been shown to start cell signaling cascades which end with nerve death in the brain. Full body blast test animals have shown an increase in certain molecules linked with nerve cell apoptosis and cognition dysfunction. It is not fully understood if the activation of these cell signal cascades is a result of direct blast damage to the brain or a result of tissue injury in other parts of the body traveling to the brain.

Data also suggest blast overpressure can cause adverse cognitive effects resulting in executive deficit. Laboratory data have shown blast overpressure causes significant cognition dysfunction in test animals. Researchers observed a memory deficit which was linked to hippocampus damage in the brain. The memory dysfunction was also observed to be similar to that produced in other TBI models. Long term cognitive effects of blast include disturbances in attention

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and memory, and a delayed reaction time in problem solving. Veterans returning with blast injury also exhibit post concussion symptoms similar to those seen in other forms of TBI. Little is known in the mechanism relating blast overpressure and cognitive deficit.

It is recommended that an effort be continued for the MSS program to pursue definitive characterization of CNS/cognitive effects due to blast. The main reason is that any potential CNS injuries must be taken very seriously, and data have suggested a correlation between blast and cognitive dysfunction effects. It is probably true that the range of blast levels for MSS devices is much lower than those considered in the research of immediate military interest for blast injuries to the CNS, while the threshold for permanent damage is still not known. It is likely that the mechanism for cognitive effects due to MSS is at the neuronal, molecular, cellular or biochemical level as opposed to the traumatic outcomes. Field data have shown long-term cognitive effects due to blast. For non-lethal weapons, it is the immediate reversible effect that is of high interest, but any long-term effect must be avoided.

Animal models are used extensively in medical research to investigate disease states in ways which would either be inaccessible in a human patient, or by performing harmful procedures that would not be considered ethical to inflict on a human. By studying the animal we can learn more about the physical, biochemical, and behavioral changes that occur, as well diagnosis and treatment methods. However, in order to serve as a useful model, the modeled disease must be similar in etiology and function to the human equivalent. To fully investigate the mechanisms of cognitive dysfunction due to blast, large animal models will need to be used. However, performing these tests is expensive and requires special facilities. Small animal tests can be used immediately for studying mechanisms of executive deficit effects due to blast at the levels produced by current and evolving flashbang devices.

Investigations have shown that widespread neurochemical changes occur in brain regions that appear structurally normal after mild closed head injury. The latest findings using proton magnetic resonance spectroscopy (MRS) has allowed researchers to identify markers of cognitive dysfunction where the brain looks structurally normal. Studies using MRS have identified a lower N-acetyl-L-asparitic acid/creatine (NAA/Cr) ratio as a marker for cognitive decline in the aging brain, and diseases such as bipolar disorder and Alzheimer's. In the pursuit of determining the cause of combat-related posttraumatic stress disorder (PTSD), a significantly reduced NAA/Cr ratio has been identified in returning warfighters. Current research is being conducted to correlate cognitive dysfunction in returning warfighters and NAA/Cr results from MRS scans (Menon et al., 2004).

MRS analysis of small animals with mTBI have also correlated reduced NAA/Cr ratio with cognitive dysfunction. It was reported that the reduced NAA/Cr ratio after insult was reversible for mild TBI. However, a second mild insult within a short period of time (3 days) resulted in a NAA/Cr ratio change associated with severe head injury (Vagnozzi et al., 2005).

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Although, the human and small animal models both demonstrate NAA/Cr is a reliable correlate for cognitive dysfunction, it has yet to be related to blast. It is recommended that small animal tests be conducted to determine the effect blast has on small animal cognition using MRS technology. As reported in this paper, there are numerous proposed mechanisms to cause mTBI due to blast. One of the primary proposed mechanisms of causing mTBI is the rapid acceleration of the head. The authors recommend that instead of subjecting the small animals to a full body or head only blast, focusing on the effect of head acceleration will provide important correlates in controlled experimental conditions. Researchers studying mTBI in rats have demonstrated a device which accelerates the head to a degree comparable to that seen from an 800 kPa blast.

Animals subjected to a range of injury can be evaluated using behavioral tests. Cognitive function can be measured using Morris Water Maze and with NAA/Cr ratios measured using MRS. These findings can then be correlated to the acceleration used to cause injury or, using computer models, they can be correlated to species independent variables such as percent strain of brain tissue. This correlation can be used to build an injury model between blast and cognitive dysfunction in which thresholds for cognitive injury can be defined.

Injury thresholds for cognitive dysfunction in small animals can then be scaled to humans. The results can also be compared to the NAA/Cr ratio correlation with returned warfighters with PTSD when it is completed. If the results are promising and it is decided further investigation is necessary, large animal tests can then be conducted. Tests involving human volunteers must be considered very carefully in light of the small and large animal results.

The serious consequence of blast injuries to the CNS are being recognized by other government agencies, notably DARPA and MRMC, and aggressive research programs are being initiated addressing the pressing needs to protect our warfighters. The results from these new programs will likely benefit the needs of non-lethal weapon programs. Close mutual consultation and collaboration is encouraged.

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